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Article

Influence of the clinical profile of patients with refractory epilepsy on lamotrigine plasma concentration

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The purpose of this work was to evaluate the influence of the clinical profile on lamotrigine (LTG) plasma concentrations from patients with refractory epileptic seizures. In this cross-sectional study, therapeutic monitoring of LTG, and questionnaires with 75 patients with refractory epileptic seizures of a Hospital in Ribeirão Preto-SP-Brazil were performed. The multiple linear regression model was used to verify association between the LTG plasma concentrations and the independent variables. Covariance analysis was used to compare the mean LTG plasma concentration among the co-medication groups. The LTG plasma concentration was associated both with the LTG dosage (mg/kg/day) ($p=0.0096$) and with the use of first generation antiepileptic drugs (AED) ($p<0.01$), being carbamazepine (CBZ) and phenytoin (PHT), the AEDs showing the most prominent influence in reducing LTG plasma concentrations. Adverse events, adherence to the pharmacological treatment, and epileptic seizures frequency, did not show significant correlation with LTG plasma concentration values. The conclusion is that LTG plasma concentration is significantly influenced by the LTG dosage and by the concomitant use of a first generation AED.

Keywords: Lamotrigine. Refractory Epilepsy. Drug interaction. Therapeutic drug monitoring.

INTRODUCTION

Drug therapy is the first choice for epilepsy treatment in the majority of cases. Monotherapy is usually considered as the initial strategy, and despite 47% of patients having their seizures under control with only one antiepileptic drug (AED), 13% will require the association of a second AED to suppress the seizure recurrence. Consequently, 40% of the patients will continue to experience epileptic seizures in spite of adequate drug therapy, eventually being regarded as patients with refractory epileptic seizures (Kwan, Brodie, 2000; 2003).

In this context, lamotrigine (LTG) is an AED widely prescribed in association both with first and/or second generation AEDs, which favors the possible occurrence of drug interactions, since its metabolism is known to be influenced by different AEDs (Reinsberger, Dorn, Krämer, 2008; Johannessen, Landmark, 2010). Regardless of the LTG linear pharmacokinetics, its plasma concentration values show high inter-individual variability, as commonly seen in clinical practice. In addition to factors related to pharmacotherapy, there are other clinical, physiological, pathological and even demographic factors influencing the pharmacokinetic of LTG (Reinsberger, Dorn, Krämer, 2008; Patsalos *et al*., 2008).

Although there are results highlighting the existence of factors that may influence LTG plasma concentrations, such as evidence of intoxication increasing significantly with plasma concentrations above the recommended upper limit (15 mg/L) (Khinchi *et al*., 2008), the literature is not clear enough regarding the impact of these interferences and about the need for LTG therapeutic drug monitoring in clinical routine (Perucca, 2000). Therefore, there is the need to more deeply investigate the factors associated with alterations in LTG plasma concentrations and the effects of

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such alterations specifically in clinical practice, especially in Brazilian patients with refractory epileptic seizures, who are normally exposed to associations of two or more AEDs (Perucca, 2000; Rivas *et al*., 2008). Thus, the aim of the study is to evaluate the association between LTG plasma concentration and the clinical profile of patients with refractory epileptic seizures.

MATERIAL AND METHODS

Ethics approval

The protocol was approved by Ethics Committee of the Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto – Universidade de São Paulo, Brazil (HC-FMRP-USP) under the process number 8791/2010.

Study design and patients

This cross-sectional study was conducted at the Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto – Universidade de São Paulo, Brazil (HC-FMRP-USP), a tertiary care center. The selection of patients was performed from May 2011 until April 2012. The sample size was determined by non-probabilistic sampling of convenience, through saturation of invitations.

Inclusion criteria were: (i) ≥18 years old; (ii) diagnosis of refractory epileptic seizures (persistence or worsening of seizures after an attempt of two consecutive AEDs properly chosen and adequately used); and (iii) current LTG treatment, in mono- or polytherapy, for at least ten days in unchanged dosages and intake intervals. Exclusion criteria were: (i) pregnant women; (ii) patients with clinical or laboratorial evidence of liver and/or kidney dysfunctions; (iii) patients using LGT for other indications (not epilepsy); (iv) patients with cognitive impairment to answer the questionnaires; and (v) patients with LTG plasma concentration "not detectable", according to the analytical method subsequently described.

Patients on LTG treatment were identified in the hospital electronic records. After signing the written informed consent, patients received the following instructions about blood sampling: fast for 8 hours prior to the sampling; blood samplings occur from 6:30 am to 9 am; any medication should be taken only after the blood sampling. After this, patients were interviewed and lastly, the patients' medical records were analyzed in search of sociodemographic, clinical and laboratorial information.

Therapeutic drug monitoring

The LTG plasma concentrations were determined by high performance liquid chromatography with ultraviolet detection (HPLC-UV). The analytical method validated for the analyses was adapted from Angelis-Stoforidis *et al.* (1999).

The blood samples were collected in 4 mL tubes using heparin, centrifuged and the plasma aliquots were stored at -20 °C until analysis (no more than one week after the sampling). For analyses, 500 µL of plasma were transferred to a glass tube and 25 µL of internal standard (5-ethyl-5-p-tolylbarbituric acid) and 1 mL of acetonitrile were added to deproteinize the sample. The whole mixture was stirred for one minute, centrifuged for five minutes at 1800 rpm, and 500 µL of the supernatant were collected and dried under air flow. N-hexane and the mobile phase, consisting of 78% acetate buffer (0.25 M, pH 4.4) with 22% organic phase (11:1 acetonitrile:isopropanol, v/v), were added to the residue, which was stirred for one minute and centrifuged for three minutes. The lower phase was then injected into the HPLC-UV system, which consisted of a LC-10AT pump, an SPD-10A UV-VIS detector set at 220 nm and a C-R8A Chromatopac integrator, all purchased from Shimadzu (Japan). The column used was a LiChroCART® 125-4 Merck column (LiChrospher® 100, RP-8, 5 µm), coupled with a LiChroCART® 4-4 Merck pre-column (LiChrospher® 100, RP-8, 5 µm). The injection volume was 100 µL, and the mobile phase flow was set at 1 mL/min.

The carbamazepine (CBZ) plasma concentrations were determined by polarized immunofluorescence.

Independent variables

The demographic variables of interest were: age, gender and body weight. Clinical data were obtained from primary (questionnaires) and secondary (registries in medical records) information sources. The information obtained through primary sources were:

- Adverse events to AED, according to the *Adverse Events Profile Questionnaire* (AEP) - validated in Brazil (Baker *et al*., 1997; Martins *et al*., 2011). The total score ranges from 19 to 75 points, with higher values corresponding to higher adverse events frequency;
- Quality of life according to the questionnaire *Quality of Life in Epilepsy-31* (Qolie-31) - validated in Brazil (Da Silva *et al*., 2007). The total score ranges from 0 to 100 points; the higher the total score, the better the quality of life;

- Drug therapy adherence according to the Morisky-Green test (Morisky, Green, Levine, 1986). The score comprises one point for questions answered as "no" and zero points for questions answered as "yes". The total score ranges from zero to four points, with higher total values reflecting a better adherence to the pharmacotherapy;
- Pharmacoepidemiological profile: the prescribed drug therapy. This data was then confirmed in medical records.

To obtain the frequency of epileptic seizures, medical comorbidities, and evidence of alterations of the liver and/or kidney functions (alterations on urea, creatinine and/or liver transaminases tests), secondary sources were used.

Statistical analyses

The AEDs were divided into different "co-medication groups" based on the presence of an enzyme inhibitor (valproate, VPA), or the presence of enzyme inducers (CBZ, phenytoin [PHT], phenobarbital [PB] or >200 mg/day topiramate [TPM]), or the presence of both inhibitor and inducer. A fourth group was composed of patients only on LTG monotherapy. Patients in any of these four groups could also receive co-medications known not to affect the LTG plasma concentrations (benzodiazepines, TPM ≤200 mg/day, oxcarbazepine, ethosuximide, gabapentin, levetiracetam and/or vigabatrin) (Johannessen, Landmark, 2010).

Covariance analysis (ANCOVA) with adjustments for gender, age and body weight was used to compare the mean LTG plasma concentration values among the co-medication groups. The paired comparisons were performed using Bonferroni's correction. Groups with a small sample size (n≤2) were not included in the comparison because of their lack of representativeness.

The multiple linear regression model was used to verify any possible association between LTG plasma concentration and independent variables of interest, namely, age, body weight, LTG dosage (mg/kg/day), frequency of epileptic seizures, AEP score and adherence. This analysis was performed considering all the plasma concentrations quantified in this study and was also performed separately, considering only the group co-medicated with enzyme inducers. The small sample size of the other therapeutic schemes (monotherapy, inhibitors, and inducers + inhibitors) did not allow the analysis separated by groups. The dependent variable was converted into a base 10 logarithm scale in order to make the residues follow normality assumption.

The Fisher exact test was used to analyze the association between adherence and LTG plasma concentrations. Pearson Correlation was used to analyze association between: LTG plasma concentration and CBZ plasma concentration, adverse event scores, and quality of life. All statistical analyses were performed using SAS (version 9.3) and R software (Brazil). The level of significance was set at 0.05 for hypothesis testing.

RESULTS

Patients' sociodemographic and clinical profiles

Among 341 patients in LTG use, 82 accepted the invitation to participate in the study, but seven were excluded because they were not in steady state or LTG was undetectable in plasma. Thus, 75 patients were included in study. The majority were adults between 18 and 60 years old (97%) and men (53%). On average, the patients' body weight was 74 kg, ranging from 48 to 145 kg (Table I).

Regarding the daily dosages of LTG, it was observed that 52% of the patients used above 300 mg/day, and 500 mg/day was the highest prevalence of use (21.3%). And 67% (10/15) of patients using LTG in monotherapy or with VPA were using doses higher than 5.0 mg/kg/day. On the other hand, 60% (34/57) of the patients in use of LTG with enzyme inducers were using LTG dosages (mg/kg/day) lower than 5.0 mg/kg/day.

Lamotrigine plasma concentrations

The LTG plasma concentration mean value was 5.4 mg/L, with 29% of the patients presenting plasma concentration values below the lower limit of the recommended range (2.5–15.0 mg/L) (Patsalos *et al.*, 2008). On the other hand, four patients (5.3%) presented LTG plasma concentration values above the upper limit of the reference range, varying between 18.5 and 25.6 mg/L.

The co-medication groups comparisons using ANCOVA with adjustments for gender, age and body weight revealed a statistically significant difference among the LTG plasma concentration values ($p<0.01$) (Figure 1).

It was also possible to verify the individual influences from AEDs on LTG plasma concentrations. As observed in Figure 2, the mean LTG plasma concentration value quantified in the monotherapy group (9.9 mg/L) was significantly different to that quantified in the group of patients using PHT (3.4 mg/L) or CBZ (3.7 mg/L). The LTG plasma concentrations from these two latter groups were, in their turn, significantly different from that

TABLE I - Sociodemographic and clinical features of the patients with refractory epilepsy using lamotrigine at AEDC of HCFMRP-USP on the period of May/2011 until April/2012 (n=75)

Variable	Enzyme Inducer Group	Enzyme Inhibitor Group	LTG Monotherapy[B]	Inducer + Inhibitor
Number of patients	57	05	10	03
Adults/Elderly[A]	55/02	05/00	10/00	03/00
Male (%)	31 (54%)	03 (60%)	04 (40%)	02 (67%)
Mean age in years (SD)	37.5 (10.6)	31.4 (9.3)	40.2 (14.3)	41.7 (3.2)
Mean body weight in kg (SD)	74.3 (16.9)	68.9 (10.4)	72.8 (23.8)	71.8 (9.5)
Comorbidities[C] (%)	20 (35%)	02 (40%)	05 (50%)	01 (33%)

[A]Adults: 18-59 years old, elderly: ≥60 years old. [B]Monotherapy, in this case, refers to the absence of enzyme inducers or inhibitors. [C]Expressed as total number of patients with at least one comorbidity. SD: standard deviation.

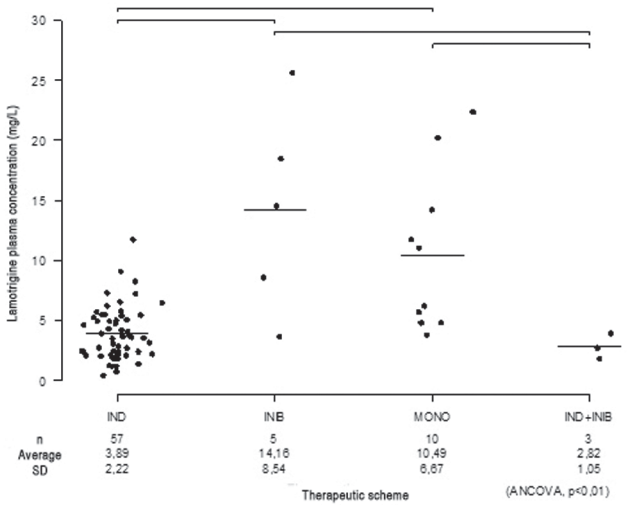

FIGURE 1 - Comparisons among the mean LTG plasma concentrations considering the co-medication groups (n=75). (IND: inducers; INI: inhibitors; MONO: monotherapy; SD: standard deviation). Horizontal lines at the top of the graph indicate pairwise significant differences between the groups.

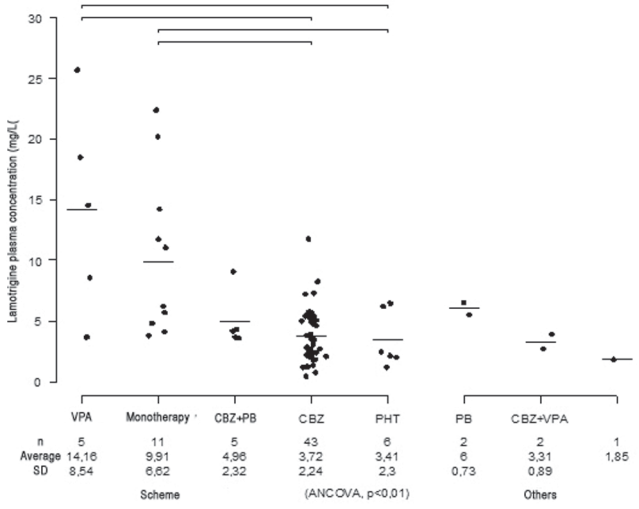

FIGURE 2 - Comparisons among the mean LTG plasma concentrations considering the specific therapeutic schemes taken by the adult patients with refractory epileptic seizures (n=75). (VPA: valproate; CBZ: carbamazepine; PB: phenobarbital; PHT: phenytoin; SD: standard deviation). Horizontal lines at the top of the graph indicate pairwise significant differences between the groups.

corresponding to the group of patients in VPA treatment (14.6 mg/L) (Figure 2).

Association between LTG plasma concentration and CBZ plasma concentration [Pearson Correlation: r = 00:09, 95% CI (-0.19, 00:35), p = 00:53] was not observed.

Adverse events

Analyzing the adverse events profile from the 73 patients who answered the AEP, it was found that the most prevalent adverse events were associated to the central nervous system, such as somnolence, difficulty in concentrating, and nervousness and/or agitation. The analysis of AEP identified that 33 patients (44%) presented a total score ≥45. There was no association between LTG plasma concentrations and AEP total scores (p=0.14).

Quality of life

Regarding the 62 patients who answered the questionnaire, the mean of the general score was 63 (SD = 8.58). The results of Qolie-31 presented, in general, low scores in all domains related to this humanistic parameter, with "concern about crisis" [37 (SD = 28.26)] and "adverse events" [46 (SD = 28.38)] being the domains that presented the highest quality of life impairment. Quality of life was inversely associated with

adverse events obtained from the AEP (r=-0.69; p<0.01) (Pearson Correlation).

Adherence to pharmacological treatment

The evaluation of adherence to pharmacological treatment from the 74 patients who answered the Morisky-Green test revealed that 45 patients (60%) presented some impairment regarding this parameter. The scores obtained by this indirect method and the respective values of LTG plasma concentrations in each subgroup were not significantly associated, according to Fisher's exact test (p=1.00).

Lamotrigine plasma concentrations and clinical response

The performance of the multiple linear regression model to assess any possible association between LTG plasma concentrations and clinical and/or pharmacotherapeutic variables highlighted that only LTG dosage (mg/kg/day) was significantly associated with LTG plasma concentration values (p=0.0096) (Table II).

The determination coefficient (R^2) of the model was 0.22, highlighting a wide dispersion of the dependent variable (LTG plasma concentration) based on the independent variables (R^2 may range from 0 to 1, with values closer to 1 corresponding to smaller variability and better fit of the tested model) (Table II).

Based on the influence of AED over LTG plasma concentrations, a linear regression analysis was conducted considering only the enzyme inducers group. The results showed that only LTG dosage (mg/kg/day) is associated with LTG plasma concentration (p=0.0116). The determination coefficient R^2 of this model displayed a higher value (R^2=0.42) when compared to the R^2 from the overall analysis (without considering co-medication).

DISCUSSION

Almost one third (29%) of the patients displayed LTG plasma concentration values below the lower limit of the recommended reference range. This result is probably associated with three main factors: non-adherence to treatment, the high prevalence of patients in use of LTG dosages (mg/kg/day) lower than the recommended (45%) and the possibility of drug interactions particularly with the enzyme inducer AEDs (Johannessen, Landmark, 2010), since 67%, 11% and 8% of the patients were taking CBZ, PB and PHT, respectively. In relation to the four patients who presented LTG plasma concentrations above the upper limit of the recommended reference range, two of them were in use of VPA.

The analysis performed considering the different co-medication groups (Figure 1) showed a wide variability in LTG plasma concentrations, with group mean values varying from 2.82 mg/L (SD=1.05) to 14.16 mg/L (8.54) when LTG was taken with "inducer + inhibitor" and with "inhibitor", respectively. As observed, the mean LTG plasma concentration seen in the "inhibitor group" was approximately four-fold higher than in the "inducers group", even with both groups presenting similar LTG dosages (mg/kg/day). Similar results were also found by Bootsma *et al*. (2008), Lalic *et al*. (2009) and Yamamoto *et al*. (2012). These results suggest that there are prescriptions that are not being individualized according to the co-medications.

Regarding the influence of AED on LTG disposition, the differences in plasma concentration values among groups are associated to the enzyme induction or inhibition

TABLE II - Multiple linear regression model of the lamotrigine plasma concentration with refractory epilepsy patients' clinical and sociodemographic variables, treated at AEDC of HCFMRP-USP between May/2011 and April/2012 (n=75) R2= 0.22

Variable	Coefficient	Standard Error	t-value	p-value
Intercept	0.15540	0.39969	0.39	0.6995
LTG dosage mg/kg/day (log_{10})	0.39755	0.14607	2.72	**0.0096**
Frequency of seizures (log_{10})	0.00235	0.08324	0.03	0.9776
AEP score	0.00259	0.00523	0.50	0.6230
Age (years)	-0.00042	0.00392	-0.11	0.9161
Body weight (kg)	-0.00005	0.00290	-0.02	0.9852
Morisky-Green test	0.10199	0.09269	1.10	0.2777
Adverse events on medical record	0.09926	0.10085	0.98	0.3309

AEP: *Adverse Events Profile*.

of the main LTG metabolic pathway (UGT1A4) caused by first generation AEDs. Carbamazepine, PHT and PB also induce CYP1A2, CYP2C9, CYP2C19 and CYP3A4 activities, as well as the glucuronyl transferases (including UGT1A4), while VPA inhibits these enzymes' activities (Perucca, 2005; Johannessen, Landmark, 2010; Brzakovic *et al*., 2012).

Analysis of the mean values of LTG plasma concentrations referred to the different individual AED groups (Figure 2), and it was observed that PHT and CBZ exerted the most prominent influence in decreasing LTG plasma concentrations. These results corroborate those from Weintraub and colleagues (2005), that revealed an increase of 125% and 50% in LTG clearance when it is associated with PHT and CBZ, respectively, while VPA decreases the LTG clearance in approximately 60% (Weintraub *et al*., 2005). In addition, May, Rambeck and Jurgens (1996) highlight that PHT is the most powerful AED in terms of decreasing the LTG plasma concentration, followed by PB and CBZ.

The present results reinforce the need, in clinical practice, to consider both the LTG dosage and co-medications when interpreting plasma concentrations information. Moreover, polytherapy is, in epilepsy treatment, a very common and unavoidable situation, which makes therapeutic drug monitoring an essential tool to manage drug interactions (Lalic *et al*., 2009).

Concerning the findings of adverse events, similar results were obtained by a study performed in the United Kingdom which identified tiredness, memory problems and difficulty in concentrating the most prevalent adverse events when patients with several types of epilepsy were analyzed, on monotherapy and polytherapy (Andrew *et al.*, 2012). In our sample, 44% of the patients presented total AEP total scores ≥ 45 points, which is according to Gilliam *et al.* (2004), a threshold associated with high risks of intoxication, and often require some clinical intervention.

The lack of association between LTG plasma concentration values and adverse events was also found by Bootsma and colleagues (2008). Faced with this evidence and the good tolerability of LTG, it is important that further studies evaluate and discuss the possibility of increasing the upper limit of the plasma concentration reference range of LTG, in relation to what is currently advocated (15 mg/L) (Patsalos *et al*., 2008). Morris and colleagues (1998) suggest that a range from 3 to 14 mg/L would be appropriate in the case of patients with refractory epileptic seizures. It is noteworthy however, that concentrations up to 20 mg/L are often well tolerated and associated with additional efficacy in refractory epilepsy patients (Patsalos *et al*., 2008). Further studies are clearly needed to re-evaluate the LTG plasma concentration reference values, especially for patients with refractory epileptic seizures, since concentrations above the upper recommended limit could be more effective in controlling epileptic seizures without compromising tolerability.

Among the limitations of the present study, it is important to highlight the reduced prevalence of patients (n=4) with plasma concentrations above the upper reference limit (15 mg/L) (Patsalos *et al*., 2008) and the impossibility to establish association between the adverse events and specific AED, because there are no patients using monotherapy. To do so, it would be appropriate to conduct a study only with patients using LTG in monotherapy.

Regarding the inversely proportional association between quality of life and adverse events ($r=-0.69$; $p<0.01$), it is in accordance with Gilliam *et al*. (2004) and Alexandre-Junior *et al*. (2011). This finding should be considered as a warning to professionals in clinical practice, since it is common for clinical and laboratorial parameters to overlap psychosocial results during therapeutic plan determination.

Besides these two relevant questions on results interpretation, it is important to highlight that a longitudinal study conducted by Kaminow *et al*. (2003) evaluating the use of LTG in monotherapy and in comparison with first generation AEDs, showed that LTG presented better results in terms of improving quality of life when compared to CBZ, PHT, and VPA (Kaminow *et al*., 2003). Viteri *et al.* (2010) also confirmed, through prospective cohort, that LTG presents a positive impact on epilepsy patients' quality of life, especially in women (Viteri *et al.*, 2010). In the present study it is not possible to associate the low scores for quality of life with the use of LTG.

Regarding the high prevalence (60%) of problems related to non-adherence to pharmacotherapy, it can also be one of the factors that contribute to the amount of patients (29%) that had LTG plasma concentrations below the recommended range. High prevalence rates of non-adherence to AEDs were also found in studies performed in Palestine (64%) (Jones *et al.*, 2006) and in the United Kingdom (59%) (Sweileh *et al*., 2011). The adherence test used was very important to investigate possible association between the indirect method of evaluation of adherence (questionnaire) and the direct method (therapeutic monitoring). Among the factors that may explain the lack of association (Fisher's exact test: $p=1.00$) it is important to highlight that there are co-medications taken with LTG, and possible biases of information during the application of the Morisky-Green test.

The multiple linear regression model (Table II) showed that only LTG dosage (mg/kg/day) is associated with LTG plasma concentrations (p=0.0096). This association can be explained by the linear pharmacokinetics of LTG (Perucca, 1996) and corroborates the findings from Krasnigi *et al*. (2010), who argued in favor of a strong association between LTG dosage and its plasma concentration values.

Lastly, it is relevant to emphasize the limitations of the present study: the doses of LTG may be affected by other classes of drugs (non-AED). However, due to lack of reliable medical records, this variable was not considered in the analysis. Furthermore, the patients do not use the same LTG dosages (mg/kg/day). Another important fact is that despite the widespread use of the Morisky-Green test in Brazil, this instrument was developed in a different context and it did not follow the procedures of cross-cultural adaptation from Brazil.

On the other hand however, the article presents results that have impacts on practice: i) for patients in use of LTG with a first generation AED, dose-adjustment by therapeutic drug monitoring is necessary; ii) clinical pharmacists and physicians need to monitor the drug interactions of LTG to avoid intoxication and/or increase of epileptic seizures; and iii) in clinical practice it is important that therapeutic drug monitoring of LTG is incorporated into the clinical routine of reference centers in refractory epilepsy.

CONCLUSIONS

The LTG plasma concentration values were shown to be associated with the LTG dosage (mg/kg/day) taken by the evaluated patients (p=0.0096), and were significantly influenced by first generation AEDs (p<0.01), being PHT and CBZ, the AEDs with higher influences on decreasing LTG disposition. Thus, the therapeutic monitoring of LTG is indicated when in concomitant use with first generation AEDs, especially at the beginning of treatment or when there is need for the medication dose change.

CONFLICT OF INTEREST

No conflicts of interest have been declared.

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